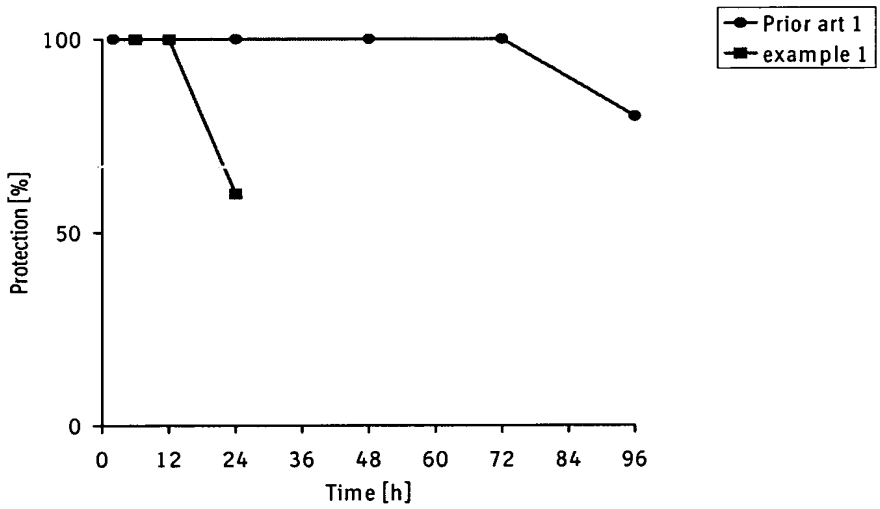
submitted in an IDS filed after the first Office Action, the instant Office Action should not have been made final. *See* M.P.E.P. § 706.07(a). Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the finality of the instant Office Action.

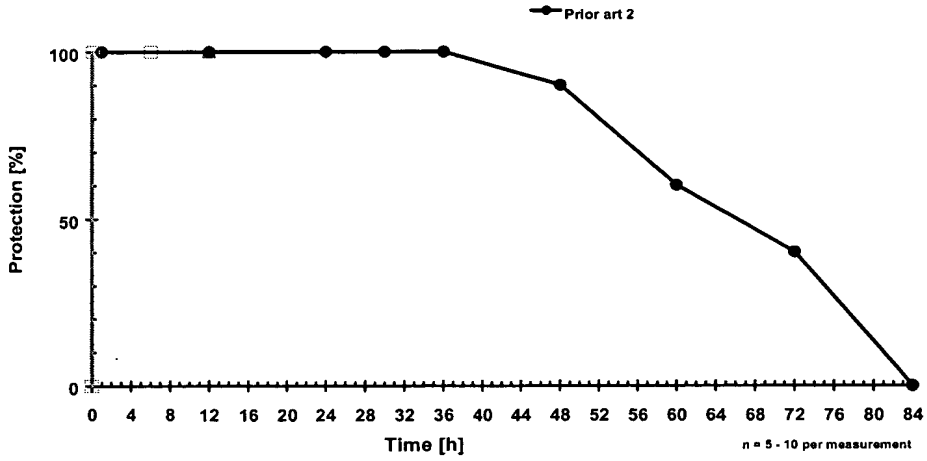
The Examiner rejected claims 1 to 12 and 19 to 35 under 35 U.S.C. § 103(a) as allegedly unpatentable over Banholzer I or Banholzer II. In addition, the Examiner imposed obviousness-type double patenting rejections of claims 1 to 12 and 19 to 35 over claims 1 to 14 of Banholzer I and claims 1 to 10 of Banholzer II.

In response, applicants respectfully traverse the Examiner's obviousness rejection and obviousness-type double patenting rejections and contend that the rejections are improper. A *prima facie* case of obviousness requires the satisfaction of three criteria: (i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; (ii) there must be a reasonable expectation of success; and (iii) the references when combined must teach or suggest all of the claim limitations. *See* M.P.E.P. § 2143.

As pointed out in the Background of the Invention section of the instant specification, it is the object of the invention to provide for antcholinergis, that can be applied once a day. Such a mode of administration is extremely advantageous over other administration regimes as it ensures an easy compliance of the patient in line to the intended therapeutic treatment. In order to be used as a medicament taken once a day, the active substance to be given must meet particular requirements. First, the onset of the desired activity should take place relatively quickly after administration of the drug and ideally should have as constant an effect as possible over a subsequent fairly long period of time. Second, the duration of activity of the drug should not substantially exceed a period of about one day. Ideally, an active substance has an activity profile such that the preparation of a drug for administration once a day, which contains the active substance in therapeutically beneficial doses, can be deliberately controlled. It has been found that the benzilic acid esters of scopine, tropenol, and tropine disclosed in WO 92/16528 (equivalent to Banholzer I and II) do not meet these stringent requirements. Because of their extremely long period of activity, which significantly exceeds the above mentioned period of about one day, they cannot be used therapeutically for administration in a single dose per day.

In contrast, the compounds according to the instant claimed invention fulfill the aforementioned requirements and have been so pointed out in the specification. For example, the comparative protective efficacy of the compounds of the claimed invention and the compounds of the prior art against acetylcholine-induced bronchospastic collapse in guinea pigs after inhalative administration of aqueous solutions containing the tested compounds (according to the Kallos-Pagel model) has been established.





Legend:

example 1 is Example 1 according to the instant claimed invention;

prior art 1 is Example 10 of Table II of Banholzer I and Banholzer II; and

prior art 2 is Example 5 of Table II of Banholzer I and Banholzer II.

Dosing: all compounds were administered at a concentration of 3 mg/mL.

The bronchoprotective efficacy of Example 1 according to the invention decreases after about 24 hours to a value of about 30%. The structurally most similar compounds to Example 1 according to the instant claimed invention are Examples 5 and 10 of Table II of Banholzer I and Banholzer II, which were all tested in the Kallos-Pagel model. It is apparent that, with identical dosing levels, both Examples 5 and 10 of Table II of Banholzer I and Banholzer II display a bronchoprotective effect of 100% even after 20 hours. This extremely long duration of action of the Banholzer I and Banholzer II compounds shows that they are not useful for a once-a-day mode of administration, in contrast to the compounds of the instant claimed invention. If the Banholzer I and Banholzer II compounds of such a long duration of action are administered once-a-day, this leads to the disadvantageous effect that the active compound is administered again when the dose applied 24 hours before is still fully effective. Consequently, the intended effect can be increased in a uncontrolled manner, which may result in undesired and harmful side effects for the patient. In contrast, as the compounds according to the invention fit into the pharmacokinetic profile necessary for a once-a-day drug, they do not display the disadvantages of the Banholzer I and Banholzer II compounds. This superiority of the compounds according to the claimed invention could not be deduced from the Banholzer I and Banholzer II compounds. If required, applicants will submit such data in the form of a Declaration under 37 C.F.R. § 1.132 in order the allow this application.

Thus, Banholzer I and Banholzer II do not provide the required suggestion or motivation to obtain the instant claimed invention, a reasonable expectation of success, or teach or suggest all of the claim limitations. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw each of these rejections.

Applicants submit that all the pending claims are allowable and respectfully solicit a Notice of Allowance for all of the pending claims. If the Examiner feels that a telephone interview would be helpful in advancing prosecution of this application, the Examiner is invited to contact the attorney below.

Certificate of Mailing Under 37 C.F.R. § 1.8(a)
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on March 21, 2003.

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3-21-2003

Dated

Respectfully submitted,

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